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Long-Term Effects of High-Protein Diets on Renal Function

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Abstract

Chronic kidney disease (CKD) has a prevalence of approximately 13% and is most frequently caused by diabetes and hypertension. In population studies, CKD etiology is often uncertain. Some experimental and observational human studies have suggested that high-protein intake may increase CKD progression and even cause CKD in healthy people. The protein source may be important. Daily red meat consumption over years may increase CKD risk, whereas white meat and dairy proteins appear to have no such effect, and fruit and vegetable proteins may be renal protective. Few randomized trials exist with an observation time greater than 6 months, and most of these were conducted in patients with preexisting diseases that dispose to CKD. Results conflict and do not allow any conclusion about kidney-damaging effects of long-term, high-protein intake. Until additional data become available, present knowledge seems to substantiate a concern. Screening for CKD should be considered before and during long-term, high-protein intake.

Contents

INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem with a global prevalence of approximately 13% (53). It is a marked independent risk factor for cardiovascular disease (64). The most frequently identifiable causes of CKD are diabetes and hypertension. In population studies, the cause of CKD is often uncertain. Experimental and some human studies have indicated that protein intake above nutritional recommendations may increase the progression of CKD (57, 74) and may have a negative impact on renal health in populations without preexisting CKD (23). It is, therefore, of concern that high-protein (HP) intake greater than 1.5 g protein/kg of ideal body weight (BW) daily has become increasingly popular in the western world for weight reduction, physical performance enhancement, body composition, and general good health.

A protein or amino acid load increases renal blood flow and glomerular filtration rate (GFR) quite markedly. The introduction of glomerular hyperfiltration as a possible mechanism of progression of CKD (16) suggested that HP intake may be harmful to the kidneys. Low-protein diets were prescribed for CKD patients. The diets had limited or no effect on renal disease progression and always carried a risk of malnutrition (39).

What is the ideal dietary protein intake? The answer might depend on not only the protein amount but also the protein source. In observational studies, red meat protein has been associated

with negative effects on the kidneys, whereas such associations have not been found for white meat and dairy proteins, and fruit and vegetable proteins may have a protective effect (7, 83, 85, 86). However, people who consume high amounts of red meat generally weigh more, smoke more, and are less physically active, so the risk of residual confounding is high.

In this review, we give an overview of the current knowledge on the possible damaging renal effect of HP intake and of some protein sources, and we focus mainly on long-term effects in the healthy population; in patients with diseases that predispose to CKD, such as diabetes and obesity; and in patients with established CKD. We also discuss aspects of the pathogenesis and pathophysiology of CKD as well as important methodological issues in the evaluation of renal function during HP intake. To facilitate the understanding of these issues, we briefly describe the normal kidney and age-dependent changes in renal function. We do not address issues related to children, which are beyond the scope of this review.

PROTEIN INTAKE

Recommendations

Health authorities have set guidelines for dietary composition and recommended intakes of nutrients, including protein, in the general population and in various specific groups. Dietary patterns in the western world have changed toward more protein intake, which may be higher than recommended (23). A safe upper limit for protein intake has not been defined.

General population. The World Health Organization (WHO) (129) recommends a dietary intake of 0.83 g good quality protein/kg BW/day. Good quality protein is defined as protein with a protein digestibility-corrected amino acid score (PDCAAS) value of 1.0. Use of the PDCAAS is a method of evaluating protein quality on the basis of the amino acid requirements that the protein satisfies and on the digestibility of the protein. A PDCAAS value of 1.0 is the highest quality and 0 the lowest.

The US recommendation, established in 2002 by the National Academies Institute of Medicine (now named the Health and Medicine Division) (58), is an intake of 0.8 g good quality protein/kg BW/day for healthy adults of both sexes and at all ages. The recommendation includes a macronutrient range of intake for protein that contributes 10–35% of energy consumption (E%). The European Food Safety Authority (33) also recommends an intake of 0.83 g good quality protein/kg BW/day.

Elderly. In the 2012 Nordic Nutrition Recommendations (98), recommendations are given according to age. Thus, 10–20 E% for protein is recommended in adults aged 18–64 years and 15–20 E% in elderly persons ≥65 years. These ranges of E% correspond to 0.8–1.5 and 1.1.–1.3 g protein/kg BW/day, respectively. The PROT-AGE Study Group (8), an international study group reviewing dietary protein needs with aging, similarly recommends an average intake in the range of 1.0 to 1.2 g protein/kg BW/day.

Athletes. A slightly higher protein intake of 1.2–1.7 g/kg BW/day is recommended for athletes who train for endurance and strength (5). Protein supplements are not recommended for athletes who consume a variable mixed diet or for healthy adults who perform regular physical activity (8).

Diabetes. The 2017 Standards of Medical Care in Diabetes (4) recommend no adjusting of the previously recommended daily level of protein ingestion (typically 1–1.5 g/kg BW/day or 15–20 E%). Protein intake goals are recommended to be individualized based on current eating

patterns. For type 2 diabetes meal plans, including slightly higher levels of protein (20–30 E%) may contribute to increased satiety. For those with diabetic kidney disease, dietary protein should be maintained at 0.8 g/kg BW/day.

Chronic kidney disease. International renal guidelines recommend 0.8 g protein/kg BW/day in adults with GFR <30 mL/min/1.73 m^2 and avoiding intake >1.3 g/kg BW/day in adults with CKD at risk of progression (69).

High-Protein Diets

HP diets have a protein content of more than 25 E% of energy intake, which corresponds to more than 2.0 g protein/kg BW daily. Examples of HP diets are Atkins (29 E%) and Zone (35 E%) diets (29). HP diets can induce increased weight loss and improve weight maintenance after weight loss (25, 80, 108). Furthermore, these diets are effective at improving glycemic control and other markers of cardiovascular risk in type 2 diabetes (6, 43). In a single study, HP intake surprisingly prevented the weight loss–induced fall in insulin resistance (116). Recently, a 6-month randomized controlled trial in 24 individuals showed remission of prediabetes with an HP diet, as well as significant improvement in metabolic parameters and anti-inflammatory effects as compared with a high-carbohydrate diet (117). A potentially harmful effect of HP intake is increased blood pressure, as indicated by measurements of daytime ambulatory blood pressure in a cross-sectional study of 121 patients with type 2 diabetes (92), possibly because HP diets are associated with increased salt intake.

Dietary Sources of Protein

Almost all food of plant and animal origin contains protein. Pulses, such as nuts, dried peas, and lentils, have HP content. Meat, fish, milk, and eggs have large quantities of good quality protein. Meat is typed as red or white according to its source: Beef, pork, mutton, and game (e.g., reindeer and moose) are generally defined as red meat, and chicken and turkey are defined as white meat (98).

Diet is a major determinant of the acid load that must be excreted by the kidney to maintain acid-base balance. Some products, such as meat, fish, cheese, and rice and other grains, are generally relatively strong net-acidifying foods, whereas fruit, legumes, vegetables, and potatoes are relatively strong net-alkalinizing foods (7).

Studies that explore whether animal and vegetable proteins differ in their effects on normal and diseased kidneys yield conflicting results. For instance, a study compared the effect of a single meal of tuna fish or boiled egg white in six healthy individuals and six type 2 diabetics without albuminuria. Tuna fish caused a rise in measured GFR in both study groups, whereas boiled egg white, which has the same or double the amount of protein, did not change GFR (96). In another study of six healthy volunteers, single meals of 200 g of beef and a similar amount of vegetable protein (baked skim soy with soy sauce, which has an amino acid composition similar to beef) caused a similar rise in measured GFR (100). Intervention studies of patients with type 2 diabetes and microalbuminuria that compared diets with animal or plant protein have shown conflicting measured GFR and urinary albumin excretion results (46, 128).

Several mechanisms have been suggested to explain a possible difference between vegetable and animal proteins with regard to renal health. These mechanisms include differences in postprandial circulating hormones, sites of protein metabolism, and interaction with accompanying micronutrients and prostaglandins (10). Furthermore, catabolism of animal proteins generates acid, whereas catabolism of many fruit and vegetable proteins forms bases (102). Acid-inducing

diets may cause kidney tubular toxicity by a mechanism that has not yet been fully clarified (127). In addition, a diet with a high dose of animal proteins might be associated with an increased salt intake and an increased tendency to urolithiasis, both of which tend to increase renal damage.

Recent observational studies have supported an importance of meat type and dietary acid load (7, 83). These studies are discussed below.

Protein Supplementation

Protein supplementation is widely used for patients during convalescence and for patients who have chronic diseases or are elderly with poor appetite. However, it is also widely used by people who eat sufficiently. The market for protein supplementation is unregulated and unsupervised by public health authorities in most countries. In the general population, advice about protein supplementation is probably mainly given by nonhealth professionals. The products range from milk protein (whey or casein) to proteins from vegetables, chicken, and red meat.

Assessment of Dietary Protein Intake

Dietary protein intake may be estimated by measuring urinary urea or nitrogen excretion or by self-reporting food intake via 24-h dietary recall, a food diary, or a food frequency questionnaire (FFQ).

Urea is the main catabolite of dietary protein. It is excreted in the urine, and at steady state, protein intake can be calculated from urinary urea excretion (91). Urinary nitrogen measurement offers an alternative calculation. Although these methods of evaluating protein intake are objective, they reflect the intake over only a few days before urine collection and give no information on protein source intake or other macronutrients.

The dietary recall may identify the pattern of eating with a minimum of reporting bias. A 3- or 4-day food diary contains a complete record of foods and beverages consumed over those days. The FFQ is widely used to investigate food intake over extended periods of time. An abbreviated assessment obtaining only the frequency of typically consumed foods is especially useful in identifying healthy foods, which can be grouped, but is not as useful in identifying unhealthy and processed foods, which are ubiquitous in every food category. Some FFQs have been validated (51, 130), but questionnaire-based methods are associated with both random and systematic error (71).

NORMAL RENAL FUNCTION

In young adults, the average number of glomeruli per kidney is 600,000–1 million (30, 99). Each nephron consists of a glomerulus and its connected tubulus system. Nephrons develop in the fetal kidneys during 10–36 weeks of gestation and may continue to develop in infants born very early preterm (104). Intrauterine malnutrition and low-protein intake may negatively influence nephron development (22). A low nephron endowment at birth is a risk factor for CKD and cardiovascular disease later in life (88). As part of the aging process, almost half of the nephrons are lost from young adulthood to old age (30, 99).

GFR in young adults is 80–120 mL/min, conventionally corrected to a body surface area of 1.73 m^2. Most of the filtered substances are reabsorbed in the tubules, but some, such as creatinine and potassium, are secreted by the tubular cells. GFR is autoregulated and thus constant during wide blood pressure changes (111). It varies over the day, presumably because it is stimulated by protein intake with meals. GFR is lowest during the night (12). It declines with age approximately proportionally with the loss of nephrons (104), presumably modified by hyperfiltration in the

remaining nephrons attempting to maintain a normal GFR. In a recent population study, measured GFR fell 0.95 mL/min/year (34). The age-dependent GFR decrease might be particularly marked in patients with heart failure (36).

Normally, minimal amounts (less than 30–50 mg/24 h) of plasma proteins, mainly albumin, are excreted in the urine. Albuminuria is associated with endothelial dysfunction and is a risk factor for loss of renal function, cardiovascular disease, and premature death. Even slight albuminuria has been associated with an increased risk of cardiovascular disease and death (54, 73).

ASSESSMENT OF KIDNEY DAMAGE

In clinical practice, kidney damage is mainly evaluated by renal function and proteinuria or albuminuria. Renal function is synonymous with GFR. When studying the long-term renal effect of dietary or pharmacological intervention, whether it is beneficial or harmful, the most relevant endpoints are death and development of end-stage renal disease (ESRD). However, more commonly used parameters are albuminuria or proteinuria and some GFR marker. Renal biopsy is an invasive procedure that is used mainly for diagnostic purposes in selected patients and in smaller scientific studies. New potential biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), have arisen with the promise of detecting kidney damage earlier than is possible with the currently used markers. Neither NGAL nor other new biomarkers for CKD have been verified for clinical use (87).

Measurement of GFR

Substances that are filtered freely in the glomeruli and not reabsorbed or secreted in the tubuli include the polyfructose inulin, ^{51}Cr-ethylenediamine tetraacetate (EDTA), and the iodinated x-ray contrast agents iothalamate and iohexol. Renal clearance of these substances with timed urine collection is identical to GFR, but it is a rarely used method. More commonly used are simplified plasma clearance methods based on measurement of the GFR marker in plasma 4–5 h or later after injection of the marker.

Creatinine-Based Methods

Plasma creatinine is used in daily clinical work to evaluate GFR. Creatinine is formed as a result of the spontaneous degradation of a small amount of muscle creatine (1–2% per day). Differences in creatinine production among individuals and over time in a single individual may occur secondary to changes in either muscle mass or dietary protein intake. A marked rise in serum creatinine has been observed after eating cooked beef or pork (19, 59).

Clearance of endogenous creatinine, previously widely used to evaluate GFR, overestimates GFR by approximately 10% because of tubular creatinine secretion and requires an accurately timed urine collection, which may be problematic (103). The sensitivity of a reduction in creatinine clearance in detecting a reduction in GFR has been found to be only 75% (109), and the correlation between GFR and creatinine clearance is poor (94). Creatinine clearance has been generally replaced by estimated GFR (eGFR), which is calculated according to formulas that take into account an individual's serum creatinine, age, gender, and ethnicity. Based on data from the Modification of Diet in Renal Disease (MDRD) Study, an eGFR equation was developed (81), which has been widely used, but it overestimates GFR values greater than 60 mL/min/1.73 m^2. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (82) equation is superior when GFR is greater than 60 mL/min/1.73 m^2. The Cockroft-Gault formula is no longer recommended.

Important sources of error in creatinine-based eGFR include:

- Extremes of muscle mass—very high or very low—in bodybuilders, amputees, and people with pareses, muscle wasting diseases, and low body mass index (<20 kg/m^2)
- Extremes of body size
- HP intake
- Creatine supplement intake (69)

Thus, protein intake in the hours before assessment of eGFR may be a confounding factor (24). In obesity, surface correction of both measured and estimated GFR by any method carries the risk of error, especially during marked weight loss (62).

Cystatin C–Based Methods

Cystatin C is a protein produced by all nucleated cells. It is filtered freely in the glomeruli and completely catabolized by the tubular cells (1). Plasma cystatin C is not influenced by muscle mass and is, therefore, preferable in subjects with a low amount of muscle tissue (31). Some factors other than renal function do influence plasma cystatin C. These include increased age, high body mass index, smoking, plasma albumin, high plasma CRP, high-dose corticosteroid treatment, and hyper- or hypothyroidism (41, 75).

The MDRD equation has been modified by the factoring in of cystatin C, leading to a precise formula for eGFR calculation (57, 112, 118).

Evaluation of Changes in Renal Function and Proteinuria or Albuminuria

In research, either sequential GFR values or individual GFR slopes (GFR versus time plot) may be compared between study groups. The latter method is advantageous for studies in which follow-up time varies because some participants withdraw (68). GFR is a dynamic parameter that can be altered by hemodynamic maneuvers, and a GFR decrease does not necessarily reflect renal damage. Thus, some interventions, such as a low-protein diet and renin-angiotensin system (RAS) blockade, cause an initial hemodynamically mediated change in GFR, which is reversible (67, 72). It is also essential to distinguish between *measured* and *estimated* GFR. Studies using precise GFR measurements are methodologically superior to studies using eGFR.

Proteinuria and albuminuria are generally expressed as the urinary excretion rate. The reference method of a 24-h specimen remains unchanged, but an untimed urine sample with measurement of urine albumin-to-creatinine ratio (UACR) is an accepted alternative.

GLOMERULAR HYPERFILTRATION AND RENAL FUNCTIONAL RESERVE

Animals and human studies have shown that oral protein intake and amino acid infusion increase renal blood flow and GFR (55). The increase in GFR is called hyperfiltration. Hyperfiltration is also present in pregnancy, diabetes, obesity, severe burns, and renal disease. No single definition of hyperfiltration has been agreed upon (52). The maximal rise in GFR during hyperfiltration is termed renal functional reserve (14), which can be exhausted in CKD, presumably because loss of nephrons leads to hyperfiltration in remaining ones (13).

Glomerular hyperfiltration has been suggested to have harmful long-term effects on renal health. This idea was proposed in 1948 by Addis (2) and developed in 1982 by Brenner and coworkers (17), who, on the basis of rat studies, hypothesized that glomerular hyperfiltration and hyperperfusion may cause glomerular hypertension leading to glomerular damage and progressive

chronic nephropathy. As discussed below, a prolonged HP intake might contribute to this deleterious process or possibly even initiate it.

CHRONIC KIDNEY DISEASE

CKD is a general term for various disorders affecting kidney structure and function with variable clinical presentation, in part related to cause, severity, and the rate of progression. Abnormalities in kidney structure usually precede abnormalities in function. ESRD is traditionally considered to be the most serious outcome of CKD, but, most importantly, CKD is associated with substantial cardiovascular disease, even in the early stages. Thus, many patients with early stages of CKD may die from cardiovascular disease before they progress to ESRD. The excess cardiovascular morbidity partly owes to traditional risk factors, such as hypertension, dyslipidemia, diabetes, prediabetes, and insulin resistance, but other CKD-specific metabolic disturbances, such as changes in mineral metabolism, especially hyperphosphatemia, are probably of even greater significance.

CKD is classified according to level of GFR in CKD stage 1–5 and albuminuria category 1–3 (69). The lower the level of GFR and the higher the level of albuminuria, the higher is the risk for development of ESRD and cardiovascular complications.

CKD afflicts 10–15% of the population, with the majority classified as stage 1, 2, or 3, at which GFR is normal or moderately decreased (21, 49, 53). In population studies, CKD is associated with smoking, obesity, or physical inactivity, but a specific renal disease is rarely diagnosed. Patients in stage 4 frequently progress to stage 5, in which renal replacement therapy is usually needed.

Treatment of CKD aims at preventing progression to ESRD and cardiovascular complications. The most important progression promoters are uncontrolled hypertension and a high level of proteinuria. RAS blockers are particularly effective in CKD because they lower both blood pressure and proteinuria. Marked restriction of protein intake was previously used in treatment. The renoprotective effect of protein restriction is small (39) and must be balanced against the risk of patient malnutrition. A Cochrane review (38), which included studies with renal death (defined as the need for dialysis or kidney transplant or the death of the patient), found a protective effect of protein restriction. As previously mentioned, 0.8 g protein/kg BW/day is recommended in adults with GFR <30 mL/min/1.73 m^2 and protein intake >1.3 g/kg BW/day avoided in adults with CKD at risk of progression (69).

Protein-rich foods are sources of dietary phosphate. Disturbances of phosphate metabolism develop in early stages of CKD and are treated by dietary instructions and phosphate-binding agents. Metabolic acidosis is another problem in CKD because of decreased renal acid excretion. Progression of CKD has been halted by oral alkali supplementation with sodium bicarbonate (26, 90). Remarkably, dietary acid reduction with fruits and vegetables had a similar positive effect in a short-term study of CKD patients, as judged by indirect markers (44). Also, a reduction of uric acid and folic acid therapy might be beneficial (113, 133).

ACUTE RENAL EFFECTS OF PROTEIN LOADING

Watzadse (126) observed in 1928 that amino acids and peptides increased blood flow in the isolated perfused frog kidney. In Copenhagen, Moustgaard (95) fed dogs with horse meat and observed a dose-response relation between meat amount and GFR increase up to a maximum of 60–70 g meat/kg BW; higher amounts up to 100 g/kg caused no additional rise. The maximal GFR increase was approximately 80%, which was called reserve capacity. Other animal studies, mostly in rats, have shown the same renal response to protein (13). The mechanism of protein- and amino acid–induced renal hyperfiltration has not been fully clarified. Endocrine mediators with renal vasodilator properties, such as glucagon and insulin-like growth factor I, have been proposed

to be involved, as have changes in RAS activity; intrarenal mechanisms, such as tubuloglomerular feedback; and increased infiltration of immune cells in the kidney (28, 52, 70, 131).

Human studies comparing creatinine and inulin clearance in healthy nonvegetarians and vegetarians have shown that the latter had a significantly lower GFR corresponding to a low habitual protein intake. In the nonvegetarians, ingestion of 80 g of cooked red meat caused a rise in GFR starting at 2 h and peaking 30 min later. In patients with renal disease, some had a renal response to protein loading; others did not (14, 111). Intravenous infusion of amino acids had a similar effect (20).

SHORT-TERM (<6 MONTHS) EFFECT OF HIGH-PROTEIN DIET ON RENAL FUNCTION

In rats, intrauterine growth restriction was induced with an isocaloric low-protein diet. The newborn rats were given 12 weeks of a HP diet, which worsened hypertension and proteinuria as compared with a standard-protein diet (110). As pointed out in a recent editorial by Bie & Astrup (11), this and similar studies illustrate the importance of adequate nutrition in pregnancy, avoiding both very low- and very high-protein intake.

Short-term human studies in healthy subjects (15, 40, 60, 123, 125), patients with hypertension (66) and type 2 diabetes (27) and elderly people (101) have shown conflicting effects of HP intake on GFR and urinary albumin excretion. In healthy people, the effect may be related to their age.

The largest study was done in 164 healthy adults with prehypertension or stage 1 hypertension in the Optimal Macronutrient Intake (Omni-Heart) trial (66), in which the 6-week HP diet (25 E%) caused a significant mean increase in cystatin C–based eGFR of 3.8 mL/min/1.73 m^2, as compared with diets comprised of 15 E% protein. This effect was independent of blood pressure. The authors concluded that protein intake might have adverse consequences on kidney function in the long term. Interestingly, the eGFR change calculated using the creatinine-based MDRD equation was −0.8 mL/min/1.73 m^2. This probably reflects an HP-related increase in serum creatinine, and it illustrates that cystatin C is a better GFR marker than is creatinine in HP studies.

LONG-TERM (≥6 MONTHS) EFFECTS OF HIGH-PROTEIN DIETS ON RENAL FUNCTION

Experimental Studies

The renal anatomy and physiology of pigs are very similar to those of humans. In an interesting study, adult female pigs were randomized to normal protein (15 E%) or HP (35 E%) diets. At 4 months, the HP group had markedly higher measured GFR than the normal-protein group. At 8 months, the HP group had 55% more fibrosis and 30% more glomerulosclerosis, whereas there was no difference in GFR between the groups. Surprisingly, the pigs on the HP diet did not get proteinuria. The study strongly suggests that in the HP diet group protein-induced hyperfiltration was followed by the development of CKD with a fall in GFR (65). The same research group exposed rats to HP diet (35 E%) for up to 17 months, causing increased creatinine clearance, proteinuria, and structural changes in the kidneys (124). As pointed out by the authors, the proteinuric response to HP diet in rats is similar to that which may be seen in humans, whereas the response in pigs does not include proteinuria.

Observational Studies in the General Population

A number of important prospective cohort studies in the general population exist and, among these several have been published within recent years. Longitudinal observations are obviously more informative than cross-sectional ones.

The Nurses' Health Study. The effect of protein intake over an 11-year period was studied in 1,135 women, with baseline age of 55 years and eGFR ≥80 mL/min/1.73 m^2. Dietary protein intake was measured twice at intervals of 4 years using a semiquantitative FFQ. There was no significant association between protein intake and eGFR change as judged by the MDRD and Cockcroft-Gault formulas. In 489 women with baseline eGFR 55–80 mL/min/1.73 m^2, protein intake was significantly associated with a change in eGFR of −1.69 mL/min/1.73 m^2 per 10 g increase in protein intake. The effect was greatest in those with the highest intake of nondairy animal protein (74).

A later publication reported on the associations of diet with albuminuria presence and eGFR decline ≥30% over 11 years in an expanded group of 3,296 participants. Interestingly, compared with the lowest quartile, the highest quartile of animal fat and two or more servings of red meat per week were directly associated with microalbuminuria, as judged by a single UACR measurement. There was no longitudinal association of HP intake with eGFR decline ≥30%. But, as also noted by the authors, in the first study, the primary outcome was eGFR change as a continuous variable, whereas a dichotomous categorization for eGFR decline was used in the second study (86). Furthermore, eGFR calculated according to the MDRD formula has low accuracy in the normal to high GFR range, and finally, creatinine-based eGFR might overestimate GFR in elderly people with low muscle mass. This might have been the case in the second study, in which women aged 67 years had a remarkably high median eGFR of 76 mL/min/1.73 m^2.

Associations between dietary patterns and renal outcome have been studied in a subgroup of approximately 3,000 participants who had repeated dietary data. The dietary patterns were prudent (with higher intake of fruits, vegetables, legumes, fish, poultry, and whole grains), Western (with higher intake of red and processed meats, saturated fats, and sweets), and Dietary Approaches to Stop Hypertension (DASH)–style (with greater intake of vegetables, fruits, and whole grains). Compared with the lowest quartile, the highest quartile of Western-pattern scores was associated with microalbuminuria and rapid eGFR decline ≥3 mL/min/1.73 m^2/year. Women in the top quartile of the DASH score had decreased risk of rapid eGFR decline but no association with microalbuminuria. These associations did not vary by diabetes status. The prudent dietary pattern was not associated with microalbuminuria or eGFR decline. It was concluded that a Western dietary pattern was associated with increased odds of microalbuminuria and rapid kidney function decrease, whereas a DASH-style dietary pattern may be protective against rapid eGFR decline (85).

The Multiethnic Study of Atherosclerosis. The Multiethnic Study of Atherosclerosis (97), a cross-sectional analysis of 5,042 participants aged 45–84 years and without clinical cardiovascular disease, diabetes, or macroalbuminuria, showed that nondairy animal food intake was positively associated with UACR, whereas neither total animal nor total plant food intake was associated with the ratio. UACR was measured in a single urine sample.

The Prevention of Renal and Vascular End-Stage Disease (PREVEND) study. In the PREVEND study (48), a community-based cohort study, participants receive questionnaires about events and are seen at 3-year intervals. In 8,461 individuals without known renal disease and 6.4-year follow-up, the mean daily protein intake was 1.20 g/kg, as calculated from two 24-h urinary urea excretions and expressed as protein intake in g/kg ideal BW, i.e., after correcting BW to a body mass index corresponding to 22. The range of daily protein intake was 0.3 to 3.3 g/kg. Urinary albumin excretion was given by the mean of two 24-h excretions obtained during the first screening round. There was no association between baseline protein intake and rate of eGFR decline, even in 502 individuals with an eGFR <60 mL/min/1.73 m^2 or in individuals with microalbuminuria. By contrast, protein intake was significantly associated

with cardiovascular events. Compared with intermediate protein intake, individuals with either higher or lower protein intake had higher event rates. All-cause mortality and noncardiovascular mortality were also associated with protein intake. Individuals with low-protein intake had the highest event rates. The methodology in this study is good. However, the lower accuracy of eGFR in the normal to high GFR range when using the MDRD formula might have influenced results. Longer follow-up data using eGFR based on the CKD-EPI equation are foreseen.

The Gubbio Study. The Gubbio Study (23), a population-based study, has investigated the association of protein intake with creatinine-based eGFR in 1,522 participants aged 45–64 years at baseline. Renal parameters were reassessed in 1,144 of the 1,425 survivors at the 12-year follow-up. At baseline, mean eGFR was 84 mL/min/1.73 m^2 (CKD-EPI), and the protein intake was 1.34 ± 0.57 g/day/kg of ideal BW, taking body mass index 22 kg/m^2 as indicative of ideal weight. Protein intake was assessed by single overnight urinary excretion of urea nitrogen. Baseline cross-sectional analyses indicated a positive correlation of protein intake with eGFR; 1 g/day higher protein intake was related to 4.7 mL/min/1.73 m^2 higher eGFR. At follow-up, the mean change in eGFR was −11.6 mL/min/1.73 m^2. Baseline protein intake correlated with more negative change in eGFR. In a multivariable regression, 1 g/day higher protein intake was related to −4.1 mL/min/1.73 m^2 more negative eGFR change and to 1.78 risk for incidence of eGFR <60 mL/min/1.73 m^2. A single overnight urinary excretion of urea nitrogen might not reflect habitual protein intake. However, owing to the long-term follow-up and good eGFR methodology, this study is of major importance.

The Dutch Generation R Study. In the Dutch Generation R Study (93), a posthoc analysis of data from pregnant women and their offspring, it was found that higher total and vegetable, but not animal, maternal protein intake during the first trimester of pregnancy was associated with a higher eGFR in the offspring at 6 years of age. The study supports rat studies, which showed that a normal, rather than low, protein intake during pregnancy is necessary to obtain the optimal nephron endowment in the offspring (110).

The Framingham Heart Study. The first findings from the Framingham Heart Study (37) showed that a healthy diet, represented by a higher Dietary Guidelines for Americans Adherence Index (DGAI) score, was associated with better kidney function or lower risk for CKD over 7 years of follow-up. A recent study examined which individual food groups were driving the association that was first observed. The primary outcome was incident low eGFR at follow-up defined as eGFR <60 mL/min/1.73 m^2 (CKD-EPI formula). Among 1,822 participants aged 59 years, 181 incident cases of low eGFR were identified. Low adherence to dietary recommendations was associated with higher odds of incident low eGFR. Low adherence to dairy product recommendations was associated with higher odds of incident low eGFR compared to optimal adherence. Rapid eGFR decline was defined as mean annual eGFR decline ≥3 mL/min/1.73 m^2. Low adherence to meat and legume recommendations was associated with rapid eGFR decline, and low adherence to dairy product recommendations was associated with rapid eGFR decline and incident albuminuria, as evaluated by UACR. As the authors concluded, these results suggest that protein intake that is either lower or higher than the optimal recommended amount may be harmful to kidney function, although it is not only protein intake that is evaluated (89).

The Cardiovascular Health Study. The Cardiovascular Health Study (9) followed 3,623 participants for 6.4 years, and registered protein intake and source at baseline from a FFQ. The eGFR was cystatin C–based and, in sensitivity analyses, creatinine was also incorporated into

calculations. At baseline, 23% of participants had eGFR <60 mL/min. Decline in eGFR was on average 2 mL/min/1.73 m^2/year. Fast loss of eGFR, defined as a decrease in eGFR of more than 3 mL/min/1.73 m^2/year, was seen in 27% of the participants. There was no association between general or rapid eGFR change and protein intake or source of food protein. The mean age of the participants at baseline was 72 years, and the average protein intake was 1.35 g/kg BW, which is equivalent to 19 E% for protein. These elderly people might have changed dietary habits during the almost 7 years from diet assessment to the follow-up. Furthermore, as discussed by the authors, participants with CKD might have been advised by their physicians to limit protein intake. Repeated administration of the FFQ during follow-up would have been of great interest.

The Singapore Chinese Health Study. In the Singapore Chinese Health Study (83), a cohort study of participants aged 45–74 years, habitual diet information was collected with an FFQ. Over 15.5 years, 951 ESRD cases occurred in 60,198 subjects. When classified according to quartiles of red meat intake, mostly pork, the red meat intake was 12.5, 24.2, 33.4, and 48.8 g/day, respectively. Participants in the highest quartile of red meat intake also had higher total protein intake, 65.3 versus 53.1 g/day, but markedly lower intake of fruits, 169.5 versus 232.8 g/day, and a minimally lower intake of vegetables, 107.9 versus 113.8 g/day. Compared with the lowest quartile of total protein intake, the three higher quartiles combined had a hazard ratio for ESRD of 1.24 [95% confidence interval (CI) 1.05 to 1.46], but there was no dose-dependent association across the quartiles. By contrast, the red meat intake was strongly associated with ESRD in a dose-dependent manner. Thus, the hazard ratio for highest versus lowest quartile of red meat intake was 1.40 (1.15 to 1.71). Intake of poultry, fish, eggs, or dairy products did not associate with risk of ESRD. Notably, total protein intake was not high, and as pointed out in an accompanying editorial (45), the strong association between red meat intake and ESRD was not confounded by increased overall protein intake. Furthermore, the low fruit and vegetable protein intake in the red meat quartile groups might have contributed to the result. Sensitivity analysis in a subpopulation without a baseline history of diabetes, hypertension, coronary heart disease, or stroke (n = 42,039), which included 25% of ESRD cases, showed no clear association of ESRD risk with total protein intake; however, intake of red meat showed a strong dose-dependent association with ESRD risk in this group of individuals without these comorbidities. The same positive association with red meat was observed in participants with at least one of these underlying comorbidity risk factors for ESRD. The study provides important information on the effect of protein intake source—and fruit intake—both in the general population and in individuals with preexisting comorbidity associated with high CKD risk. It is more difficult to draw a conclusion regarding the effect of total protein intake per se.

Studies on Cardiovascular Outcome. In large cohort studies with 10–15 years follow-up, low-carbohydrate HP diets have been associated with an increased risk of cardiovascular disease (77, 78, 114, 122). No renal data are reported in these studies. Because even early stages of CKD are associated with an increased risk of cardiovascular disease, it might be speculated that the observed increased cardiovascular risk might be explained by increased CKD. However, in another study, a low-carbohydrate diet was not associated with coronary heart disease after 20 years follow-up (50).

Studies in Populations with Preexisting Disease

The influence of protein intake on renal health has been studied in patients with various preexisting diseases that increase the risk for CKD and in patients with established CKD. Most of the studies are intervention trials, but some are prospective cohort studies.

Obesity. In obesity, there are several randomized trials on the renal effect of dietary protein. In a 6-month study of 65 obese individuals, aged 39 years, fat-reduced diets with protein amounts of 1.6 g/kg BW (25 E%) and 1.0 g/kg BW (12 E%) were compared. All food was provided to the participants. Protein intake was validated by 24-h urinary nitrogen excretion. Weight loss was greater in the HP diet group. Measured GFR rose by 8.8 mL/min in the HP group and fell by 4 mL/min in the low-protein group. Kidney volume increased by 9.1 cm^3 in the HP group and decreased by 6.2 cm^3 in the low-protein group. 24-h urinary albumin excretion, measured at 0, 3, and 6 months, was normal (115). These results are compatible with hyperfiltration induced by HP intake and fall in GFR induced by low-protein intake, as also seen in the MDRD trial (72). The authors interpreted the changes as adaptive alterations. The fact that urinary albumin excretion did not increase in the HP group does not exclude the possibility that renal damage could develop during longer HP intake.

A study in 100 obese subjects, aged 49 years, compared the effect of two isocaloric weight meal plans, providing 2.2 versus 1.1 g protein/kg of lean body mass. Meal replacement, that is, meals replaced with products containing defined nutrients, was used twice daily for 3 months and then once a day for 9 months. There were no differences in changes in 24-h creatinine clearance, serum creatinine, or urea nitrogen within the groups and between the groups. Urinary protein excretion increased in the standard protein group, but the change in proteinuria was not different between the groups (84). The study is limited by lack of GFR data, only two measurements of proteinuria, and many withdrawals. Also, adherence to diet can be questioned, as there was no difference in urinary nitrogen.

In a 1-year study of 68 abdominally obese subjects, aged 52 years, an energy-restricted, planned isocaloric very-low-carbohydrate (35 E% protein, 124 g) diet was compared with a high-carbohydrate diet (24 E% protein, 85 g). There were no changes in either group in creatinine-based eGFR. Normoalbuminuria did not change (18). It is noted that initially 118 participants were randomized but 49 dropped out, and data are thus given only for the remaining participants. Renal parameters were evaluated only two times.

A secondary analysis of a study in 307 obese adults, aged 46 years, compared a low-carbohydrate HP diet with a low-fat weight-loss diet for 24 months. Of the participants, 15% had microalbuminuria at baseline. The HP diet was associated with minor reductions in serum creatinine and cystatin C levels at 3 months only and increases in creatinine clearance at 3 and 12 months. These changes indicate hyperfiltration caused by the low-carbohydrate HP diet. At 24 months there was no difference in these parameters between the groups. Urinary albumin excretion was unchanged. Serum urea was higher in the HP group as expected owing to increased protein metabolism. It was concluded that the low-carbohydrate HP diet was not associated with noticeably harmful renal effects, but further follow-up is needed to determine even longer-term effects on kidney function. We agree that hyperfiltration might have caused a loss of renal reserve. As also stated by the authors, the study had some limitations, including lack of GFR measurements and data on diet adherence, such as urea excretion (42). Furthermore, the proportion of missing data was high, in that only 51% of participants had blood analysis and only 40% had urinary analysis at 24 months.

The long-term effect of various diets, particularly a low-carbohydrate HP diet, on renal function was also addressed in the 2-year Dietary Intervention Randomized Controlled Trial (DIRECT), which compared low-fat, Mediterranean, and low-carbohydrate diets in 318 participants, aged 51 years, with a mean eGFR of 71 m/min/1.73 m^2 (CKD-EPI). Renal function was evaluated at baseline, 6 months, and 24 months. The compliance was 85%, and the proportion of protein intake increased to 22 E% only in the low-carbohydrate diet group. In all diet groups, eGFR increased with similar magnitude. The increased eGFR was independent of type 2 diabetes and baseline eGFR above or below 60 mL/min/1.73 m^2. UACR decreased similarly across the diets

(121). It would have been interesting if GFR had been measured accurately. It is rarely seen that renal function improves in patients with CKD stage 3, which occurred in this study.

Type 2 diabetes. Studies in type 2 diabetes on the renal effect of dietary protein include both observational studies and randomized trials.

Observational studies. In a recent cross-sectional observational study in patients with normal renal function, microalbuminuria was associated with HP intake (3). By contrast, two previous cross-sectional studies found no relationship between protein intake and albuminuria in patients with type 2 diabetes (61, 119).

Randomized trials. A 12-month study of 99 obese patients with type 2 diabetes, aged 30–75 years, compared low-fat diets that were high either in protein (30 E%) or in carbohydrate (55 E%). Among secondary endpoints were changes in blood pressure, creatinine-based eGFR, and urinary albumin excretion rate, which did not differ between the groups (79). Notably, even though the study achieved a significant group difference in 24-h urea excretion at 3 months, the difference was not significant at 12 months, which causes us to question the results. No information was given about the formula used to calculate eGFR.

A blind 12-month study of 419 individuals with type 2 diabetes and normal renal function (of whom 18–19% had increased UACRs) compared low-fat HP and low-fat high-carbohydrate diets (protein E% 30 versus 15). A further assessment was undertaken 12 months after the intervention. Among secondary outcomes were renal function and blood pressure. Protein intake was evaluated by self-reported food diaries. There was no change in serum creatinine, UACR, or blood pressure in either group (76). However, only 6% of the HP group achieved the prescribed target protein intake, which limits the results.

A similar study of 65 patients with type 2 diabetes and microalbuminuria evaluated weight-loss diets with moderate protein, 90–120 g/day, or standard protein, 55–70 g/day, for 12 months. Only 45 patients completed the study. The average difference in protein intake was 19 g/day. No effect was seen on albuminuria or blood pressure in either group. There was no significant difference in measured GFR changes between the groups. However, in the moderate-protein diet group, GFR values were 143 and 129 mL/min at baseline and at the end of the study, whereas in the standard-protein diet group, GFR values were 112 and 113 mL/min, respectively (63). As noted in an accompanying editorial by Workeneh & Mitch (132), the fall in GFR in the moderate-protein group may have represented loss of kidney function rather than correction of hyperfiltration. It appears that data were not analyzed according to the intention-to-treat principle, and given the described power calculation, the study was underpowered.

Another study of 115 obese type 2 diabetes patients, aged 58 years, compared a low-carbohydrate (protein 28 E%, fat 58 E%) and a high-carbohydrate (protein 17 E%, fat 30 E%) weight-loss diet combined with supervised exercise training for 12 months. Completion rate was approximately 70%. Protein intake was 120 and 96 g/day, respectively, as judged by 24-h urinary urea. Changes in eGFR (CKD-EPI) and 24-h urinary albumin excretion, measured at weeks 0, 24, and 52, were very small and did not differ between the groups. Also, as stated by the authors, it is a limitation that GFR was not measured (120).

An observational follow-up study in a subpopulation of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) (32) included 6,213 type 2 diabetic patients with normoalbuminuria or microalbuminuria. eGFR, as calculated by the MDRD and CKD-EPI formulas, and albuminuria, were determined at baseline, 2 years, and 5.5 years. Diet was assessed at baseline using an FFQ. After 5 years, 32% of participants had experienced

the combined renal endpoint of incidence or progression of CKD, and 8.3% had died. Patients in the highest tertile of total and animal protein intake had better renal outcomes compared with participants in the lowest tertile.

Metabolic syndrome. In a 12-month study of 110 obese subjects assigned to either a HP (1.34 g/kg BW) or a conventional protein (0.8 g/kg BW) diet, subjects kept 3-day food records at baseline and every third month. Of the participants, 67% completed the study. Plasma creatinine did not differ compared to baseline or between groups. Subjects in the HP group had significantly higher plasma urea, reflecting a higher protein intake (35). Because of the lack of GFR data, the study does not allow any conclusions to be drawn.

Chronic kidney disease. An association between protein intake and long-term change in eGFR has been observed in participants in the Nurses' Health Study with mild CKD (74). Similar results have been observed in CKD cohort studies. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study (47) is a prospective cohort study in black and white US adults. In 3,972 participants with CKD (defined as eGFR <60 mL/min/1.73 m^2 or UACR ≥30 mg/g at baseline), dietary patterns were identified using an FFQ. Over a 6-year period, 816 of the participants died, and 141 developed ESRD. A dietary pattern characterized by fried foods, organ meats, and sweetened beverages was associated with higher mortality, whereas a higher consumption of fish, fruits, and vegetables was associated with a lower mortality risk. There were no associations of dietary patterns with incident ESRD, but the study might have been underpowered to detect such associations.

In a cross-sectional study from Taiwan that included 599 adult patients with CKD stage 3–5, energy and protein intakes were assessed using 24-h dietary recall. The Cockcroft equation was used to calculate eGFR. Compared with moderate- and low-protein intake, HP intake, defined as a ratio of actual intake to recommended intake ≥110%, was associated with worsening eGFR at increments of −3.50 mL/min/1.73 m^2. Low-energy intake was also related to GFR decreases. It was concluded that lower energy and higher protein intakes than recommended may be associated with deteriorating renal function (56).

A recently published prospective CKD cohort study examined the development of ESRD and its association with dietary acid load in 1,486 subjects enrolled in the US National Health and Nutrition Examination Survey (7). Using information from 24-h dietary recall questionnaires, dietary acid load was estimated as net acid excretion. Approximately 20% of participants developed ESRD during 14.2 years of follow-up. Higher levels of dietary acid load were independently associated with markedly increased risk of ESRD. The relative hazards were 3.04 (95% CI, 1.58 to 5.86) for the highest tertile and 1.81 (0.89 to 3.68) for the middle tertile compared with the lowest tertile. The risk of ESRD associated with dietary acid load tertiles increased as eGFR decreased. Among participants with albuminuria, high dietary acid load was strongly associated with ESRD risk. Even for a shorter duration of follow-up, <6 years, a much greater risk of ESRD was seen with high dietary acid load. Meat, fish, cheese, and rice and other grain products are generally relatively strong net-acidifying foods, whereas fruit, legumes, vegetables, and potatoes are relatively strong net-alkalinizing foods. The authors concluded that the study may have important public health implications.

Meta-Analyses

In their meta-analysis, Santesso and coworkers (105) aimed to assess the benefits and harms of HP diets compared with lower-protein diets in the general population. Participants in the 74 included studies were either healthy, overweight, obese, or hypertensive, or they had elevated

lipid levels. The intervention period had to be 28 days or more. As compared with lower-protein diets (18 E%), an HP diet (27 E%) caused small but significant falls in body mass index, waist circumference, blood pressure, and triglyceride levels. Renal parameters are very sparse; serum creatinine levels were measured in six studies. Data from two studies at 3 months, which included only 67 patients, were pooled and showed a significant increase in serum creatinine between diets, with a mean difference of 6.14 μmol/L. The other four studies reported nonsignificant changes in both diet groups. Urinary protein excretion was not reported.

Schwingshackl & Hoffmann (106, 107) have published two meta-analyses in this field. The first analysis of studies with a minimum of 12 months of diet intervention included 2,000 subjects from 15 trials (106). Renal parameters were reported only in a few studies in this meta-analysis, and no change was found in GFR. Some patients with type 2 diabetes were included, and they showed no change in serum creatinine and microalbuminuria with an HP diet. The authors concluded that HP diets cause neither benefit nor harm, but they found it premature to recommend such diets in the treatment of obesity.

In the second meta-analysis (107), which investigated renal parameters in 2,160 obese subjects from 30 trials, intervention time was 1 week to 24 months. A HP diet caused a significant rise in GFR, plasma urea, and urinary calcium excretion, whereas urinary albumin, urinary protein excretion, and plasma creatinine were unchanged. On the basis of their study, the authors cautioned against using HP diet as a treatment of obesity.

CONCLUSION AND FUTURE DIRECTIONS

In recent years, large prospective cohort studies in the general population have extended our knowledge about relations between diet and CKD. Some—but not all—of these studies suggest that long-term intake of dietary protein above nutritional recommendations can increase the risk of serious CKD, including ESRD. High intake of red meat protein and acidifying protein seems to be most harmful. However, observational studies can examine only associations, which do not necessarily signify causation, and results remain subject to the lack of control for unmeasured, imprecisely measured, or unmeasurable confounders. Some randomized trials have been undertaken with an observation time greater than 6 months in patients with preexisting diseases that predispose to CKD or with established CKD in an early stage. None of these trials have had a renal primary endpoint. Results conflict and do not allow any conclusions to be made about a kidney-damaging effect of long-term HP intake.

It is difficult to make recommendations in the absence of conclusive results. Nonetheless, until additional data become available, the present knowledge seems to substantiate a concern about HP intake above 1.5 g protein/kg of ideal BW daily. Intake of fruit, vegetable, and chicken-based protein and the avoidance of red meat may be generally advantageous, but confirmation of this statement awaits further studies. Decisions for individual patients, such as obese persons and type 2 diabetics, have to be based on a balance of evidence for and against the advantage and safety of HP intake. Because CKD is often a silent disease, screening for CKD should be considered during long-term HP intake. The renal impact of HP intake for limited periods is most likely different than that for more chronic consumption, but we cannot see any reason for such a diet in healthy people and given the potential harm, HP intake should be avoided. Likewise, we advise against HP diets for patients with CKD.

Considering the increasing prevalence and serious outcome of CKD, even in the early stages, as well as the high costs of treatment, future research on the renal effects of HP intake and different protein sources will certainly continue the work presented in this review. In the general population, ongoing prospective cohort studies will continue to provide important information as follow-up

time lengthens. Particularly, the large community-based studies with repeated screenings of diet and kidney function are likely to increase our knowledge about potential harmful renal effects of dietary HP intake and of certain protein sources. Large randomized studies in the healthy population will probably not be conducted, because they would be difficult to carry out and extremely expensive. However, it would be possible to perform randomized studies in select groups of healthy people, for example, in individuals who have an HP intake for expected improvement in their physical performance.

In patients with preexisting diseases, such as type 2 diabetes and obesity, that increase the risk of CKD, long-term, well-designed randomized controlled trials of various aspects of dietary protein are highly needed. The outcomes in these studies would have to be the likely positive effects on weight loss, blood pressure, and insulin resistance, as well as the potential negative renal effects. Change in GFR would have to be judged by accurately measured GFR at least 2–3 times during the study. Additionally, renal function must be evaluated by eGFR and UACR every 3–6 months. The dietary interventions must be followed by diet self-reporting and urinary urea measurements. Most importantly, other parameters known or thought to influence the development and progression of CKD must be controlled. These parameters include blood pressure, RAS blockade, BW, metabolic acidosis, and dyslipidemia and, in diabetic patients, glycemic control and the choice of antidiabetic drugs. Such studies need to be conducted in multidisciplinary study groups. On the basis of our present knowledge, HP studies should not be done in patients with CKD, but randomized controlled studies of various dietary protein sources must be undertaken.

The main unanswered questions in this field are whether an HP intake for many years can cause CKD in healthy people or can push patients with CKD stage 1 to higher stages. Is red meat truly the culprit, as suggested by some observational studies, and is plant protein truly renoprotective on a population level?

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Annual Review of Nutrition

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Contents

Indexes

Errata

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